# Mortality benefits of influenza vaccination in elderly people: an ongoing controversy

Lone Simonsen, Robert J Taylor, Cecile Viboud, Mark A Miller, Lisa A Jackson

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**National Institute of Allergy and Infectious Diseases** (L Simonsen PhD) **and Fogarty International Center** (C Viboud PhD, M A Miller MD), **National Institutes of Health, Bethesda, MD, USA; Department of Global Health, School of Public Health and Health Services, George Washington University, Washington, DC, USA** (L Simonsen PhD)**; LTS Corporation, Bethesda, MD** (R J Taylor PhD)**; and Group Health Center for Health Studies, Seattle, WA, USA** (L A Jackson MD)

Correspondence to: Dr Lone Simonsen, Department of Global Health, School of Public Health and Health Services, George Washington University, Washington, DC 20037, USA. Tel +1 202 416 0422; fax +1 202 416 0084; **iphlxs@gwumc.edu**

**Influenza vaccination policy in most high-income countries attempts to reduce the mortality burden of influenza by targeting people aged at least 65 years for vaccination. However, the effectiveness of this strategy is under debate. Although placebo-controlled randomised trials show influenza vaccine is effective in younger adults, few trials have included elderly people, and especially those aged at least 70 years, the age-group that accounts for three-quarters of all influenza-related deaths. Recent excess mortality studies were unable to confirm a decline in influenza-related mortality since 1980, even as vaccination coverage increased from 15% to 65%. Paradoxically, whereas those studies attribute about 5% of all winter deaths to influenza, many cohort studies report a 50% reduction in the total risk of death in winter—a benefit ten times greater than the estimated influenza mortality burden. New studies, however, have shown substantial unadjusted selection bias in previous cohort studies. We propose an analytical framework for detecting such residual bias. We conclude that frailty selection bias and use of non-specific endpoints such as all-cause mortality have led cohort studies to greatly exaggerate vaccine benefits. The remaining evidence base is currently insufficient to indicate the magnitude of the mortality benefit, if any, that elderly people derive from the vaccination programme.**

## Introduction

Influenza epidemics occur almost every winter in the USA. These epidemics cause illness in about 5–20% of the US population,[1,2] and lead to approximately 300 000 influenza-related hospital admissions and 36 000 influenza-related deaths annually.[3,4] Except during pandemic seasons, about 90% of all influenza-related deaths occur among people aged at least 65 years.[5,6]

Influenza vaccines have convincingly been shown to be effective in preventing influenza infection in healthy adults.[7] In 1960, US health authorities adopted a policy of targeting influenza vaccination efforts to those at high risk for severe outcomes, including people with chronic conditions and elderly people.[8–10] Similar policies have been adopted in most other high-income countries and have been endorsed by WHO.[11] Vaccination coverage of US elderly people has risen substantially in recent decades, from approximately 15% in 1980 to approximately 65% by the mid-1990s.[12]

Although current policy emphasises vaccination of elderly people, the evidence that this strategy effectively reduces influenza-related mortality in that age-group is weak. Placebo-controlled randomised clinical trial (RCT) data indicate that vaccination effectively prevents influenza illness in younger, healthy elderly people, but no RCT data conclusively show a similar benefit in those aged 70 years or more, the age-group that accounts for nearly all influenza-related deaths.

In the absence of so-called gold-standard RCT data, the evidence base consists mainly of observational studies that compare mortality risks in self-selected groups of vaccinated and unvaccinated elderly people. Many of these studies have concluded that vaccination reduces winter-season mortality from any cause by approximately 50% in community-dwelling elderly people,[13] and even more in nursing-home populations.[14] However, such astonishing mortality benefits are simply not consistent with estimates of the influenza-related mortality burden among elderly people, as derived from national vital statistics data.[6,15]

In this Review, we examine the major findings of, and inconsistencies between, the various kinds of evidence regarding mortality benefits of influenza vaccination of elderly people. We argue that unrecognised selection bias has led cohort studies to greatly overestimate mortality benefits. The remaining evidence is not sufficient to show that vaccination substantially reduces the risk of influenza-related mortality among elderly people. We propose a framework for identifying residual bias in cohort studies, which should help to provide a clearer picture of what vaccine mortality benefits can and cannot reasonably be expected. Our objective is to move towards a better evidence base for the setting of priorities for influenza vaccination and to identify areas where further research is needed.

## National excess mortality studies and assessment of influenza-related mortality

Assessment of the number of influenza-related deaths in elderly people is a difficult task, for many reasons. What is diagnosed as an influenza-like illness is often caused by a respiratory virus other than influenza. Moreover, influenza is often a precipitating factor that brings about death from secondary bacterial pneumonia or underlying chronic disorders,[16,17] which are usually identified as the cause of death.

Influenza-related mortality is therefore traditionally assessed by use of an indirect but robust approach that attributes to influenza all excess deaths above an expected winter baseline. This approach was first used in 1847 to characterise an influenza epidemic in London, and was further developed and extensively used throughout the 20th century.[18] Excess mortality occurs when the mortality rate rises significantly above the expected seasonally variable baseline (figure 1).[19] Because pneumonia and influenza deaths rise by a substantial percentage during most influenza epidemics, seasonal excess pneumonia and influenza mortality estimates are the best indicators of the relative severity of influenza epidemics. However, because many influenza-related deaths are attributed to causes other than pneumonia and influenza, seasonal excess all-cause mortality is the best available estimate of the total burden of influenza-related deaths.[20]

A recent analysis of excess all-cause mortality found that, since the 1968 pandemic, influenza has accounted for an average of about 5% (about 32 000 deaths; range 0·4–10%) of approximately 600 000 annual winter deaths (December through March) among the US elderly population of 31 million,[6] which corresponds to an incidence of one influenza-related death per 1000 elderly people every winter. That estimate of the burden of influenza-related mortality among US elderly people is in close agreement with a study done by the US Centers for Disease Control and Prevention that applied a different statistical model to estimate influenza-related mortality in the same population over much of the same period.[3] Influenza deaths contribute a small proportion of all winter mortality (figure 1). Influenza vaccination cannot reasonably be expected to do any more than eliminate this excess (influenza-related) mortality.

Age-specific risk of influenza-related (excess) mortality increases exponentially after the age of 65 years.[3,6] For example, people aged at least 80 years in the USA are at about 11 times higher risk than those aged 65–69 years. Moreover, in seasons between 1990 and 2001, an average of 76% of all influenza-related deaths occurred among people aged 70 years or older, and 55% among people 80 years or older.[6]

Despite an increase in vaccination coverage from 15% to 65% since 1980, crude excess mortality among elderly people actually increased during the 1980s and 1990s.[3,6] One of these studies adjusted the influenza-related mortality estimates for increases in median age of the elderly population and the greater incidence of severe type A/H3N2 influenza seasons that occurred in later years.[6] However, that study could not document a reduction in influenza-related deaths coincident with the increased vaccine coverage (figure 2).[6] Nor could it document a mortality increase in the 1997–98 season, during which the vaccine components were completely mismatched with circulating strains.[21]

Studies of trends in excess mortality are sometimes discounted because they do not rely on the vaccination status of individuals,[22] even though trends studies of this sort are commonly used to show the successes of other vaccine programmes.[23] However, it is precisely because national excess mortality studies include the entire elderly population that they have the advantage of not being subject to selection bias.[24] Moreover, the fact that a study on Italian elderly people also found no

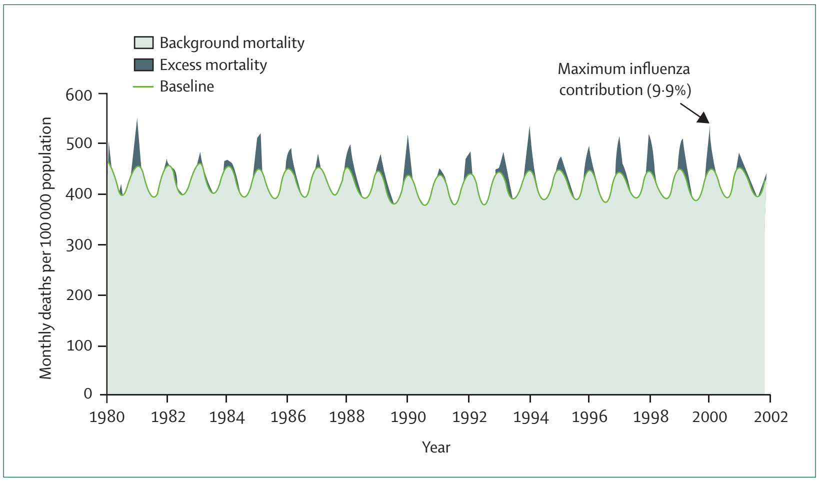


*Figure 1:* **Monthly national all-cause mortality rates in all US elderly people aged 65 years or more, 1980–2001**
The total winter-seasonal fraction of mortality attributed to influenza in national excess mortality studies averaged 5%, and was always less than 10%. Based on data from Simonsen et al.[6]

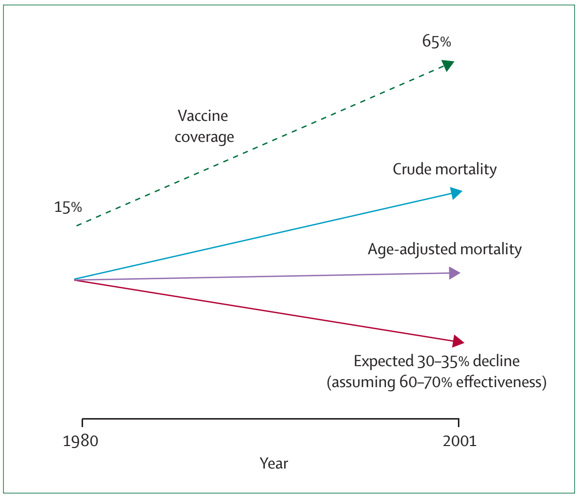


*Figure 2:* **Crude and age-adjusted trends in vaccination and national excess pneumonia and influenza mortality in US elderly people aged 65 years or more**
Data are for 13 influenza A (H3N2)-dominated seasons as vaccine coverage rose from about 15% to about 65% (dotted line). The point estimates of excess mortality trends (crude and age-adjusted, solid lines) are shown, as presented in Simonsen et al.[6] The lower bound of the 95% CI for the trend is –18%, which excludes the expected decline of 30–35% (lower solid red line), assuming 60–70% effectiveness against influenza-related mortality. This study type is not powered to exclude the possibility of more limited mortality benefits.

decline in influenza-related mortality rates, even as vaccine coverage rose from 5% to 65% in that population, should further boost confidence in the finding.[15] However, this study type is not statistically powered to rule out a relatively modest mortality benefit, and a mortality reduction corresponding to 30% vaccine effectiveness would not have been detected by this study design. Nevertheless, the unexpected failure to show a reduction in mortality over time in at least two countries raises questions about the mortality benefits to vaccinated elderly people.

| | Results from a large RCT[27] | | Results from national excess mortality studies[6]* |
|---|---|---|---|
| | Proportion of 1838 member study population (%) | VE for laboratory-confirmed influenza illness (95% CI) | |
| ≥60 years | 100% | 50% (35% to 61%) | 84–90%† |
| 60–69 years | 70% | 57% (33% to 72%) | 7–14%‡ |
| ≥70 years | 30% | 23% (–51% to 61%) | 76% |
| ≥80 years | 4% | .. | 55% |

Vaccine efficacy (VE) estimates from a placebo-controlled randomised clinical trial in a group of younger, healthy elderly people.[27] The VE point estimates suggest VE declines with age after 70 years, but the 95% CIs were wide. This study contributed no information on VE in elderly people ≥80 years, an age-group that accounts for about 55% of all US influenza-related deaths. ..=not reported. *Proportion of US excess deaths (1990–2001); percentages were estimated for each age-group from all-cause excess mortality by methods described by Simonsen et al.[6] †Range based on ages ≥55 years and ≥65 years. ‡Range based on ages 55–69 years and 65–69 years (no estimate available for ages 60–69 years).

*Table 1:* **Gold-standard evidence for influenza vaccine benefits in elderly people, by age**

## Randomised placebo-controlled clinical trials

Few placebo-controlled RCTs of influenza vaccine efficacy in elderly people have been done, and none have been powered to study severe outcomes, including mortality. However, because of the importance of this gold-standard type of evidence, we do include RCTs with morbidity endpoints in this Review. With the exception of one small trial,[25] placebo-controlled trials comprised healthy, relatively young, elderly people.[26–28] This fact severely limits what such RCTs can tell us about vaccine benefits to elderly people in less than robust health and to people aged 70 years or older—the age-group that accounts for most of the influenza-related deaths (table 1).

The largest and best-designed placebo-controlled RCT was done by Govaert and colleagues[27] in the Netherlands during the 1991–1992 influenza season. In that study, 1838 healthy volunteers aged at least 60 years were randomly assigned to receive either placebo or a trivalent inactivated influenza vaccine that was well-matched to circulating influenza strains. The study reported a 50% (95% CI 35–61%) efficacy for reduction of laboratory-confirmed influenza illness among the volunteers. However, this study also suggested that vaccine efficacy declines substantially with age. After stratifying by age, the investigators estimated a vaccine efficacy of 57% in people aged 60–69 years, but obtained a vaccine efficacy point estimate of only 23% (with 95% CI including zero) for people aged 70 years or older (table 1). That result, the investigators noted, “suggests that the effect of vaccine may decrease after the age of 70 years”.[27] They could not fully assess that possibility, however, because the study population was relatively young: 70% of participants were younger than 70 years, and 96% were younger than 80 years. The investigators’ expressed concern is often disregarded because the 95% CI for the older age-group was wide, so that the single finding generally cited from this trial is a vaccine efficacy of 50% in people aged 60 years or older.[10]

The likely reduction in vaccine benefits with advancing age reported in the study by Govaert and colleagues[27] is consistent with immune senescence, that is, a decline in immune responsiveness late in life.[29–31] In a companion study, Govaert and colleagues[32] found a protective antibody titre in 43–68% of the vaccinated study participants. However, because these data were not stratified by age, we cannot tell whether the observed reduction in clinical vaccine efficacy with age was also associated with weaker antibody responses; it would be extremely informative if these key data could be further analysed to address this question. Finally, a recent quantitative review of placebo-controlled trials of antibody responses to inactivated influenza vaccines found that elderly people respond about one-quarter to one-half as vigorously as do younger adults;[33] however, data published from these studies are insufficient to discern whether antibody responses continue to decline after 65 years of age.[33] Although a few additional placebo-controlled trials of influenza vaccination in elderly people can be found in the literature,[26,28] none resolve the problematic scarcity of clinical trial data from those aged over 70 years.

For the lower-specificity outcome of influenza-like illness, Govaert and colleagues[27] found no significant vaccine benefits in any age-group. The point estimate of the vaccine efficacy against this outcome was only 20% in people aged 60–69 years, and only 4% in people 70 years or older, with confidence intervals overlapping zero. Their finding is consistent with the theoretical principle that as the specificity of the outcome decreases, so should measured vaccine benefits.[34,35] We will return to this issue in the context of the plausibility of results from observational cohort studies.

Because influenza vaccination is now widely recommended for elderly people, setting a placebo-controlled RCT in this population would in many countries no longer pass ethical review. The scarcity of gold-standard RCT data places greater weight on evidence from cohort and other observational studies.

## Cohort studies of influenza vaccine benefits

Cohort studies of influenza vaccine effectiveness can be divided into two distinct types. Before 1990, cohort studies were usually prospective and done in nursing homes, had laboratory-confirmed primary endpoints, and used laboratory surveillance data to define the influenza season. Additionally, these earlier cohort studies often reported on less specific outcomes, such as death from any cause, even though the number of deaths among study participants tended to be small. A quantitative review of cohort studies published before 1990 concluded that influenza vaccine reduced the total risk of winter death from any cause by 68% among institutionalised elderly people (table 2).[14]

More recently, many cohort studies have retrospectively analysed large electronic health-care databases to determine the effect of vaccination on elderly people who are living in the community.[13,36,37] These studies generally defined the winter influenza period as the 4-month period from December through March, and include much larger study populations. They generally do not rely on laboratory-confirmed influenza endpoints, and often use mortality from any cause—a highly non-specific outcome—as a primary endpoint. Investigators usually seek to correct for selection bias by using multivariate models to adjust for health-status covariates defined by diagnostic codes. Two recent quantitative reviews of cohort studies concluded that vaccination reduces the risk of winter death from any cause by about 50% among community-dwelling elderly people aged over 65 years (table 2).[13,36,37]

### Selection bias in cohort studies

We find it peculiar that the claims that influenza vaccination can prevent half—or more—of all winter deaths in elderly people have not been more vigorously debated. That influenza vaccination can prevent ten times as many deaths as the disease itself causes is not plausible. A few recent cohort studies have addressed this paradox directly, and investigated the possibility that unrecognised bias has led to overestimated vaccine benefits.[38–41]

Using data from general clinical practices in England and Wales, Mangtani and colleagues[41] sought to correct for bias by comparing mortality benefits when influenza was circulating with those obtained during the peri-influenza period (the adjacent months). Although benefits from vaccination would be expected to be limited to the period during which influenza actually circulated, that was not the case when all-cause mortality was the outcome studied. Instead, the observed risk ratio (RR; also known as relative risk) comparing mortality among vaccinated and unvaccinated elderly people was the same in the influenza period (RR 0·8) as it was in the peri-influenza periods (RR 0·8). Using the latter estimate as a measure of baseline mortality differences in the study population, the investigators concluded that the adjusted vaccine effectiveness for preventing all-cause mortality was 0% in this population. However, they did find a 12% vaccine effectiveness against death from respiratory diseases, a more specific outcome. Another UK study sought to control for residual bias by comparing mortality risk in vaccinated and unvaccinated elderly people during and after the influenza epidemic period.[13,36] But that approach was based on the assumption that the baseline risk of death was constant over time after the influenza vaccination period. As we discuss below, that assumption is probably not valid.

More recently, two studies have irrefutably shown the existence of a substantial residual bias in cohort studies, identified its source, and quantified the impact on vaccine effectiveness estimates.[39,40] Jackson and colleagues[39] began by doing a conventional analysis of data from a health maintenance organisation database that reproduced the frequently reported estimate of an approximately 50% reduction in all-cause winter mortality in vaccinated versus unvaccinated elderly people over time.[38] Next, by stratifying the data by time before, during, and after the period that influenza circulated, the investigators showed that the mortality reduction occurred before the onset of influenza season and became less pronounced with time throughout the 10-month study period (consequently, vaccine effectiveness declined over time, because vaccine effectiveness equals 1–RR; figure 3). That result was inconsistent with the expected pattern, in which the greatest difference in the two groups (the lowest RR) would occur during the peak influenza period (figure 3), and thus clearly showed that the unvaccinated group was more likely to die than the vaccinated group for reasons not related to influenza. The investigators repeated the exercise by use of pneumonia and influenza hospital admissions, a more specific endpoint (figure 3), and again obtained a similar pattern.[39] They concluded that the magnitude of the bias detected was sufficient to account entirely for the observed benefit of 50% mortality reduction during the winter period.

Jackson and colleagues[40] also found that a method commonly used in cohort studies to adjust for bias—based on covariates defined by groupings of International Classification of Diseases (ICD) disease codes and indicators of medical use[42]—does not achieve the desired effect. If that method successfully adjusted for the inherent differences between vaccinated and unvaccinated elderly people, then the adjusted RR of death in the period before influenza season would be 1·0.[40] Instead, Jackson and colleagues[40] found that the method produces the paradoxical effect of further increasing the difference in mortality risk between the vaccinated and unvaccinated groups in the months

| | Study description | Study population, age, and living situation | Estimated vaccine effectiveness against all-cause mortality | Implied proportion of all winter deaths attributable to influenza* |
|---|---|---|---|---|
| **All-cause deaths (low specificity)** | | | | |
| Gross et al[14] | Quantitative review of cohort studies (before 1990) | Institutionalised elderly people ≥65 years | 68% | >68% |
| Vu et al[13] | Meta-analysis of electronic cohort studies (after 1990) | Community-living elderly people ≥65 years | 50% | >50% |
| Rivetti et al[36] | Cochrane review | Community-living elderly people ≥65 years | 47% | >47% |
| **All-cause excess deaths (high specificity)** | | | | |
| Simonsen et al[6] | US excess mortality trends study | Total US elderly population ≥65 years | 0% | 5% |
| Rizzo et al[15] | Italian excess mortality trends study | Total Italian elderly population ≥65 years | 0% | 4% |

*For cohort studies, the implied proportion of all winter deaths that are attributable to influenza is greater or equal to the measured vaccine effectiveness against mortality (assuming influenza vaccine is not perfect and can only prevent a subset of influenza-related deaths).

*Table 2:* **Vaccine effectiveness estimates and winter deaths attributable to influenza across multiple observational (cohort) studies in elderly people**

before the influenza period. The reasons for that failure are complex, but are generally related to the fact that ICD codes are not accurate indicators of severe illness and frailty, the main confounders of the association between vaccination and risk of death.[40] These findings indicate that the cohort study results are strongly influenced by uncontrolled bias. Consequently, the extraordinary mortality benefits that those studies have attributed to influenza vaccine are, unfortunately, illusory.[43]

## Towards a stronger evidence base

We have argued that cohort studies asserting that influenza vaccination can reduce winter mortality by approximately 50% cannot possibly be correct. This problem was also highlighted in a recent Cochrane review and an editorial.[36,44] We suggest two factors have caused this substantial mismeasurement.

The first of these is frailty selection. We hypothesise that a small subset of under-vaccinated and very frail elderly people contributed a substantial proportion of the total winter deaths studied. If under-vaccination were a direct consequence of these individuals' poor health status, it would be a major source of bias. Two studies found that most influenza-related deaths occurred in small subsets of under-vaccinated US and Canadian elderly people who were admitted to hospital during the autumn,[45,46] whereas a theoretical study showed the serious adverse consequences of frailty selection bias.[47]

The second factor is low specificity. We argue that the use of highly non-specific endpoints, such as winter mortality from any cause, magnified the degree to which bias skewed the estimates of vaccine benefits (see below). The combined effect of these two factors has produced a high degree of mismeasurement, leading to greatly inflated estimates of how well influenza vaccination protects elderly people from influenza-related mortality.

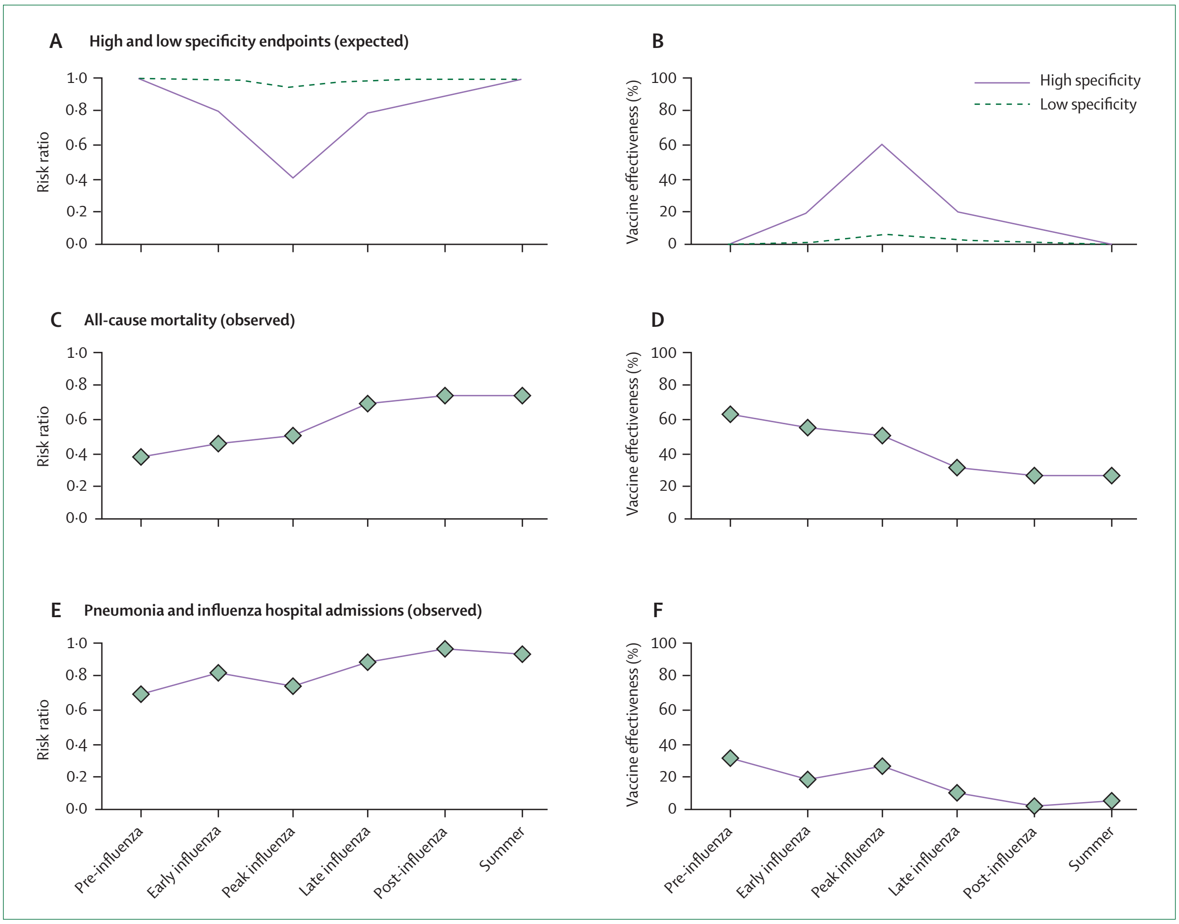


***Figure 3:*** **Use of seasonality to detect substantial bias in cohort studies**

Expected and observed seasonal patterns of risk ratio (RR) and vaccine effectiveness (VE=1–RR) in cohort studies (based on Jackson et al[39]). In the absence of residual bias, the expected pattern for a highly specific outcome would be that RR=1·0 outside influenza periods and shows (A) a substantial dip during peak influenza periods (solid line)—and consequently (B) a vaccine effectiveness measurement of 0% outside influenza periods and a peak measurement during peak influenza periods. For a low-specificity endpoint, the same pattern would be expected, albeit with a less pronounced change during the influenza peak period (A, B; dotted line). By contrast with expectations, the observed seasonal patterns based on a cohort study of (C, D) all-cause mortality and (E, F) pneumonia and influenza hospital admissions suggested lowest RR and highest VE in the pre-influenza period, thus indicating substantial bias.[39]

## An analytical framework to detect residual bias

Self-selection bias is a potential problem for all observational studies. We propose an analytical framework to identify bias in cohort studies of influenza vaccine benefits by use of any one or more of five possible criteria (table 3, panel). If any of these expectations are not met, unadjusted bias should be strongly suspected. We outline the expectations for each of the five proposed framework components in table 3 (seasonality, vaccine match, severity, age, and specificity; see panel). For most published cohort studies where we could evaluate presence of unadjusted bias using one of the framework components, the expectations were not met.

Unfortunately, detecting bias with our framework is far easier than reliably adjusting for it. We do not recommend the use of this framework to quantitatively adjust the measured vaccine effectiveness estimates for most cohort studies. This is because the vaccine effectiveness signal for a non-specific endpoint is expected to be small, and therefore precision is an issue (table 4 and table 5). For example, Jackson and colleagues[39] found a small RR dip in pneumonia hospital admissions—a moderately specific endpoint—during the peak influenza period. But unlike Mangtani and colleagues,[41] they declined to estimate a bias-adjusted vaccine effectiveness estimate by subtracting

| | Setting of greater expected RR reduction | Setting of lower expected RR reduction |
|---|---|---|
| Seasonality | Influenza period | Pre-influenza periods |
| Vaccine match | Well-matched seasons | Mismatched seasons |
| Severity | Severe seasons | Mild seasons |
| Age | Younger people | Older people |
| Specificity | High-specificity endpoints | Low-specificity endpoints |

In the absence of selection bias, for each criterion there are defined settings in which the reduction in risk ratio (RR) is expected to be higher (and consequently the vaccine effectiveness measurements lower) than in other settings.

*Table 3:* **An analytical framework for identifying residual bias in cohort studies of elderly people**

***Panel:* Expectations when applying the five framework criteria given in table 3**

**Seasonality**

*Expect no difference in risk (RR=1·0) during pre-influenza periods between the vaccinated and unvaccinated groups*

Because the underlying heterogeneity in mortality rates in vaccinated and unvaccinated elderly people fades substantially with time (figure 3), the pre-influenza period should be used to assess the presence and magnitude of bias.

**Vaccine match**

*Expect the measured RR reduction to be least pronounced for seasons when the vaccine components were severely mismatched relative to circulating strains, and to be most pronounced for well-matched seasons*

This was suggested in the late 1980s,[48] but has not been implemented in most cohort studies. For example, even though an RCT set in young adults found no vaccine benefits for influenza illness during the severely mismatched 1997–98 season,[19] one cohort study of elderly people reported a 39% reduction in all winter deaths for that season,[41] almost certainly indicating the presence of bias. It would be helpful if cohort studies were to record and publish the degree of match for each season and location studied, but this is not always done.[36]

**Severity**

*Expect the measured RR reduction to be least pronounced for seasons with low national excess mortality and most pronounced for severe seasons with high excess mortality*

Mild seasons are usually dominated by less virulent influenza A (H1N1) and influenza B viruses, and severe seasons by influenza A (H3N2) viruses. Cohort studies tend to find similar RR estimates for seasons dominated by different subtypes of influenza viruses,[49,50] again suggesting the presence of unadjusted bias.

**Age**

*Expect the RR reduction measured in the oldest groups of elderly people to be less pronounced than that of younger age-groups, because of immune senescence*

One cohort study reported no mortality benefit in elderly people aged 65–74 years (RR=0·98), whereas those aged ≥80 years accounted for most of the benefits observed (RR=0·69),[51] a finding almost certainly indicative of residual bias. Similarly, Cochrane reviews found similar vaccine effectiveness in elderly people and younger age-groups, further suggesting the presence of bias.[7,36,52]

**Endpoint specificity**

*Expect the measured RR to be most pronounced for clinical endpoints with higher specificity, and less pronounced for low-specificity outcomes*

This follows because the proportion of the outcome that is attributable to influenza and therefore preventable with influenza vaccine increases with higher specificity. For a perfect (100% efficacious) vaccine, the measured vaccine effectiveness would be about 5% for an outcome with about 5% specificity, such as all-cause mortality, and about 90–100% for a laboratory-confirmed outcome. When the true effectiveness of a vaccine is known, the risk reduction for a moderately specific outcome (such as pneumonia deaths or pneumonia hospital admissions) is a useful measure of the vaccine-preventable proportion of an outcome of interest. But when the true effectiveness is not known—as is the case for influenza vaccine in older elderly people—the measured risk reduction can be difficult to interpret. The current cohort study evidence base for elderly people does not pass the specificity test, because the vaccine effectiveness estimates are highest (and implausibly large) for all-cause mortality and lowest for laboratory-confirmed influenza.[37]

RR=risk ratio. RCT=randomised controlled trial.

out a baseline value, citing the wide 95% CIs and uncertainty about how to assess residual bias in the pre-influenza and post-influenza periods.[39]

### A way forward

Once the unrealistic assessment that influenza vaccination can prevent half of all winter deaths among elderly people is cleared away, a new assessment of the vaccine's mortality benefits can begin. With regard to cohort studies, adjustments for selection bias may be possible, but only when medium to high specificity endpoints are used. For example, it may be possible to develop a strategy to exploit ICD-coded data to identify frail elderly people more effectively, although this has so far proven to be a difficult undertaking.[40] At a minimum, observational studies should make every effort to use the most specific endpoints available, and to identify the epidemic period for each season by use of virus surveillance data, rather than a standard 4-month period in winter. Beyond that, a commonly agreed set of standards for carrying out and reporting observational studies of influenza vaccine effectiveness would be very helpful.

It may be necessary to abandon cohort studies that rely solely on electronic databases, in favour of case-control studies with laboratory-confirmed endpoints. An opportunity to put this into practice arose in the context of a study on respiratory syncytial virus (RSV) burden set in a large cohort of elderly people admitted to hospital for respiratory illness or congestive heart failure during one of four winter seasons in 1999–2003.[54] Using a nested case-control analysis and enrolling a control group of elderly people admitted to hospital with laboratory-confirmed RSV, two of us (LS and CV) estimated a 29% vaccine effectiveness (95% CI 2–48%) for the highly specific outcome of laboratory-confirmed influenza hospital admissions.[55] This study design is likely to have avoided frailty selection bias issues, because the case and control groups were of similar age and admitted with similar respiratory conditions in winter. Although the approach is both expensive and labour intensive, it offers a greater likelihood of obtaining realistic assessments of influenza vaccine benefits in elderly people.

| | Clinical outcome |
|---|---|
| Low specificity (~5%) | All-cause mortality |
| Medium specificity | All influenza-like illnesses (without laboratory confirmation). Pneumonia and influenza mortality and hospital admissions |
| High specificity (~90%) | Laboratory-confirmed influenza (mild disease or hospital admissions)<br>Excess mortality (pneumonia and influenza or all-cause) |

*Table 4:* **Clinical items on the specificity scale**

## Conclusions

Between the paucity of RCT data and the problematic cohort studies done to date, the evidence base for mortality benefits of influenza vaccination in older elderly people is slim and not particularly encouraging with regard to the degree to which influenza vaccination protects elderly people against severe influenza outcomes. Govaert and colleagues[27] suggested that vaccine effectiveness declines sharply after age 70 years. Data from a study by Falsey and colleagues[54] suggested a vaccine effectiveness of 29% for prevention of hospital admission with laboratory-confirmed influenza.[55] The studies that used US national excess mortality data were unable to show the expected mortality reduction over the years when vaccination coverage increased by 50 percentage points. Finally, placebo-controlled RCTs find that antibody responses to influenza vaccine in elderly people are only about one-quarter to one-half as strong as responses found in younger adults.[33] Taken together, these remaining studies with high endpoint specificity and low likelihood of bias suggest that vaccine benefits are modest, although the 95% CIs are wide.

We have set out a framework for identifying bias in published cohort studies, and proposed some better design choices for future observational studies. However, given the difficulties with observational studies that we have described, it may be time to revisit the idea of doing

| | Study population and seasons | Mortality outcome studied | Vaccine effectiveness (setting) | | Reference |
|---|---|---|---|---|---|
| | | | Higher effectiveness (lower RR) is expected | Lower effectiveness (higher RR) is expected | |
| Seasonality | Community-living, ≥65 years, 1999–2003 | All-cause deaths, specific periods | 44% (peak influenza period) | 61% (pre-influenza period) | Jackson et al[39] |
| Vaccine match | Community-living, ≥65 years, 1996–98 | All-cause deaths, all season | 60% (well-matched vaccine component for 1996–97) | 39% (poorly matched vaccine component for 1997–98) | Nordin et al[42] |
| Severity | Institutionalised, ≥65 years, 1982–83 | All-cause deaths, all season | 75% (nursing homes with outbreaks) | 82% (nursing homes without outbreaks) | Patriarca et al[53] |
| Age | Community-living, 1996–2002 | All-cause deaths, all year | 2% (younger elderly people aged 65–74 years) | 31% (older elderly people aged ≥80 years) | Voordouw et al[51] |
| Specificity | Community-living, ≥65 years, 1999–2003 | All-cause deaths and pneumonia and influenza admissions, all season | 18% (pneumonia and influenza admissions) | 56% (all-cause deaths) | Jackson et al[39] |

Substantial bias was detected in all comparisons. Only one of the four studies[39] interpreted and reported their findings as evidence of residual selection bias.

*Table 5:* **Application of our proposed framework to illustrate bias in selected cohort studies**

## Search strategy and selection criteria

Data for this Review included all available clinical studies addressing vaccine effectiveness against influenza-related mortality in elderly people. We also relied on the compilation of studies identified in a recent Cochrane review of clinical trials and observational studies in elderly people, and several meta-analyses of observational studies done in recent decades in community-living elderly people and nursing-home populations. Because no clinical trials studied mortality outcomes, we included any placebo-controlled trial that had clinical endpoints. We limited the search to English language studies using the search terms "cohort study" or "observational study" combined with the term "influenza".

RCTs in elderly populations. We recognise that the use of placebo in such trials would be ethically unappealing, but head-to-head trials that test the currently used inactivated vaccine against other vaccine formulations may be feasible. If future efforts fail to correct observational studies for selection bias, then further RCTs in elderly populations may become crucial.

The possibility that vaccination of elderly people might not provide as strong protection as previously thought[44,56] should not surprise immunologists studying immune senescence,[31] who have shown that immune responses to novel antigens are seriously impaired in the oldest age-groups. Refocusing on the likely complications of immune senescence should help clear the way for more vigorous pursuit of other options for influenza control. These options include the development of more-immunogenic vaccines for elderly people,[57] use of larger doses of vaccine,[58] the combining of live and killed vaccine formulations,[59] use of antivirals in a more aggressive manner for treatment and prophylaxis,[60] and indirectly protecting elderly people through increased vaccination of transmitter populations.[61,62] Implementation of any of these alternative approaches must be accompanied by valid assessments of their effectiveness.

While awaiting an improved evidence base for influenza vaccine mortality benefits in elderly people, we suggest that this group should continue to be vaccinated against influenza. Influenza causes many deaths every year, and even a partly effective vaccine would be better than no vaccine at all. But the evidence base concerning influenza vaccine benefits in elderly people does need to be strengthened.

### Conflicts of interest

We delcare that we have no conflicts of interest.

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